

Figure 1

100
General Process for Developing and Implementing
a Regulated Biochemical Reaction Network Model

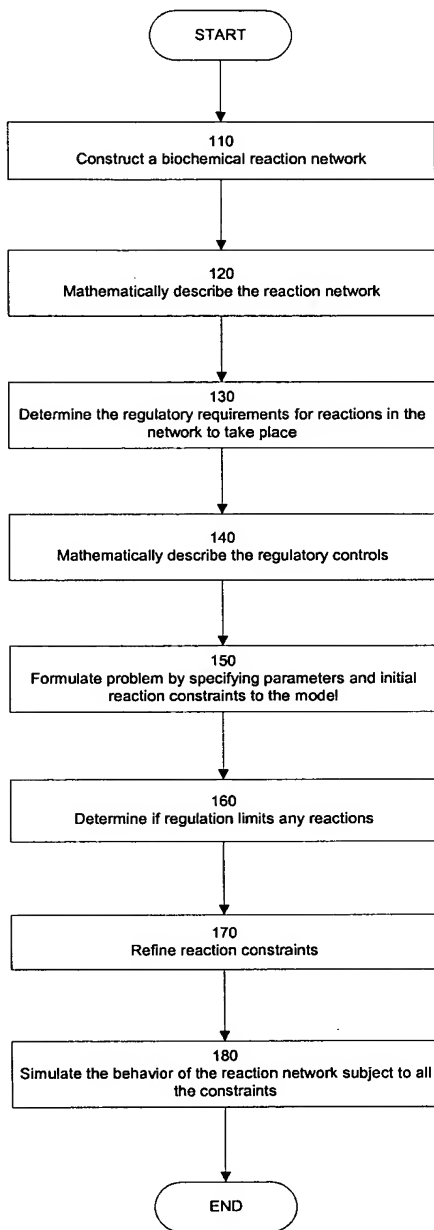
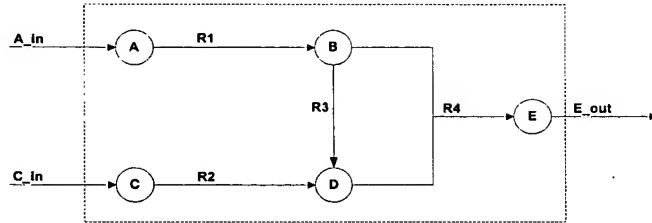


Figure 2

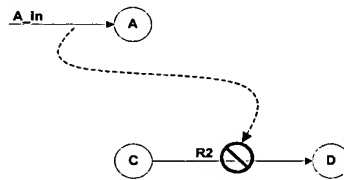
A)

Example Biochemical Reaction Network



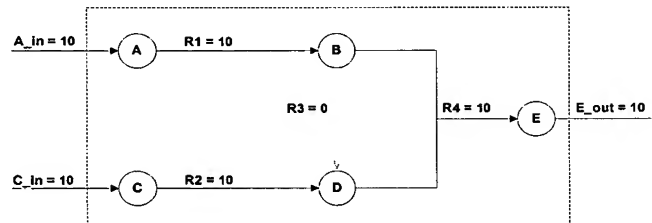
B)

Example Regulatory Structure and Requirements



C)

Simulated Reaction Network (without regulation)



D)

Simulated Reaction Network (with regulation)

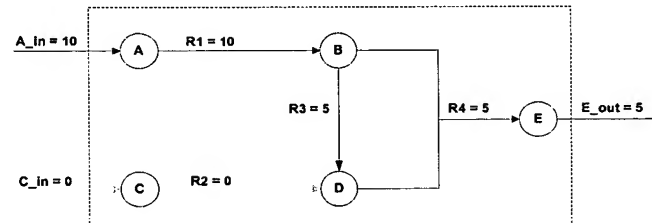
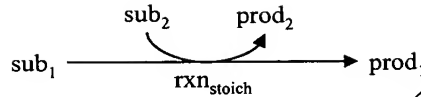
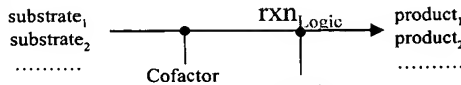


Figure 3

Metabolic Model



Regulatory Model



Activator
or inhibitor

TF

TF*

a_1

pr_1

$gene1$

$gene2$

pr_1

$gene1$

$gene2$

pr_1

$gene1$

$gene2$

pr_1

$gene1$

$gene2$

pr_1

$gene1$

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pr_1

$gene1$

$gene2$

pr_1

$gene1$

$gene2$

pr_1

$gene1$

$gene2$

pr_1

$gene1$

$gene2$

pr_1

constitutive
expression

a_2

pr_3

$gene3$

pr_3

$gene3$

pr_3

$gene3$

pr_3

$gene3$

pr_3

$gene3$

pr_3

$gene3$

pr_3

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$gene3$

pr_3

$gene3$

pr_3

$gene3$

pr_3

$gene3$

pr_3

$gene3$

- Activity constraints set for rxn_{stoich}
(lower bound = 0, upper bound = INF or #)
- Inactivity constraints for rxn_{stoich}
(lower bound = 0, upper bound = 0)

Integration of Stoichiometric model and Logical model achieved through regulatory restraints (logic values of reaction processes) which are used to refine appropriate reaction constraints in the model:

If $rxn_{Logic} = 1$ then use Activity constraints

If $rxn_{Logic} = 0$ then use Inactivity constraints

Logic functions

$a_1 = (\text{activator/inhibitor}) \cdot TF$

$a_2 = 1$

$c_1 = TF^* \cdot pr_1 \cdot gene1 \cdot gene2$

$c_2 = pr_3 \cdot gene3$

$l_1 = M_{gene1}$

$l_2 = M_{gene2}$

$l_3 = M_{gene3}$

$p1 = P_{gene1} \cdot P_{gene2} \cdot P_{gene3}$

$rxn_{Logic} = \text{Protein} \cdot \text{Cofactor} \cdot \text{Substrate}_1 \cdot \text{Substrate}_2$

Time delays can be specified for the switching of each memorization variable after a triggering change in the associated function

Figure 4

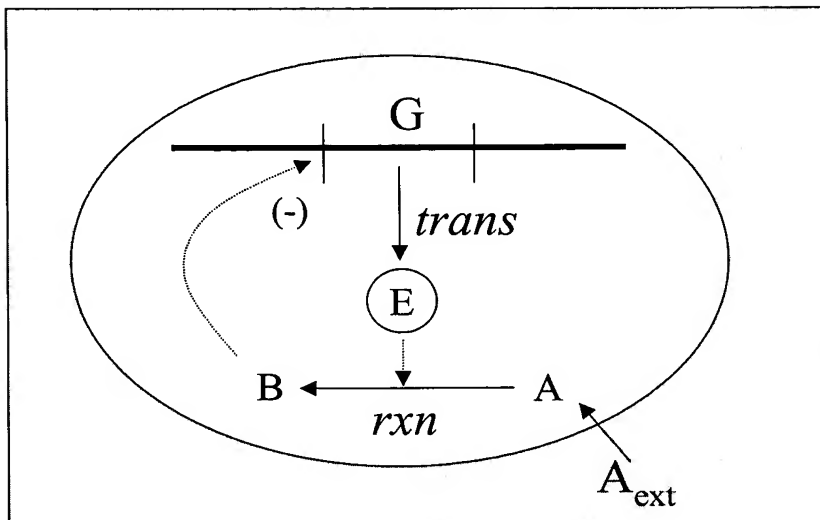


Figure 5

200

A Time-Dependent Implementation of a Regulated
Biochemical Reaction Network Model

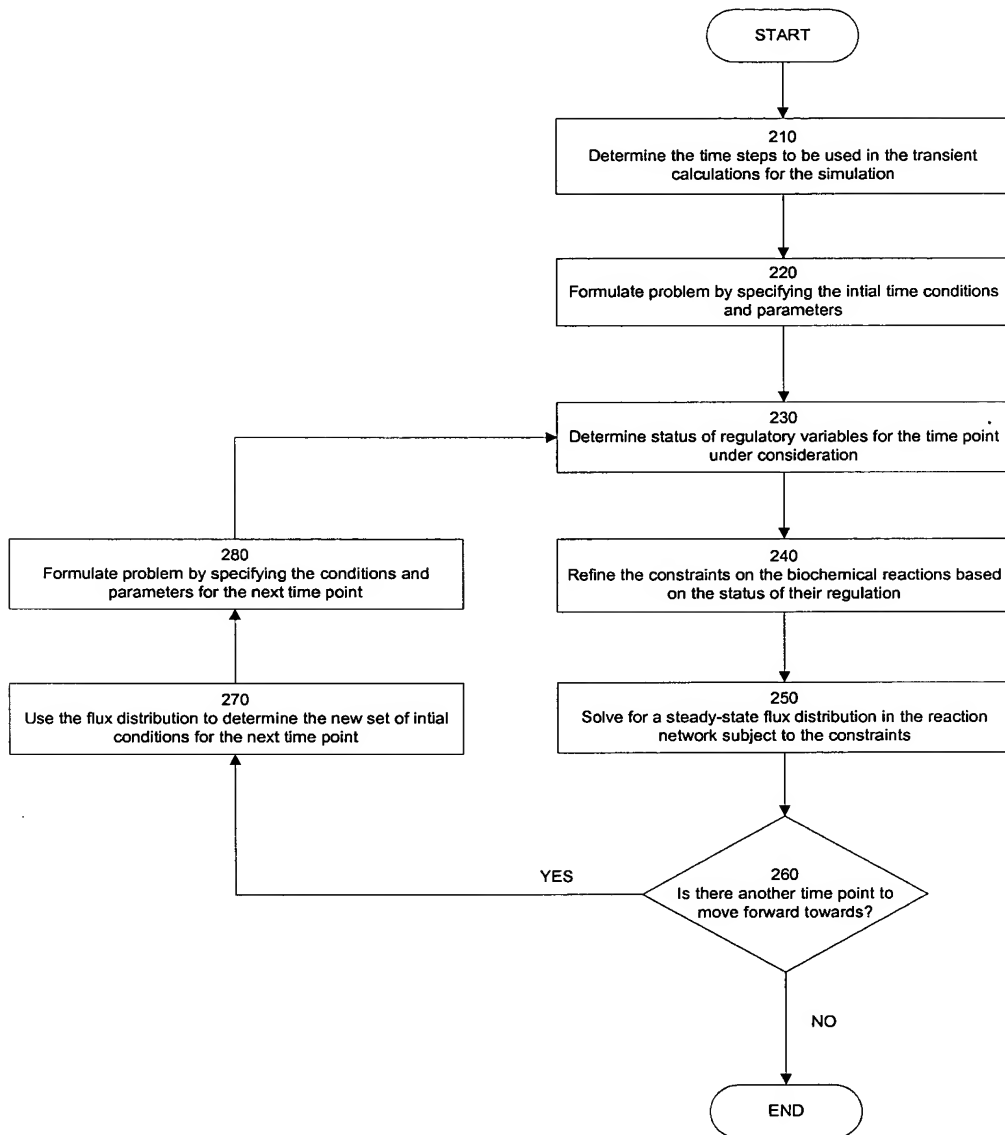
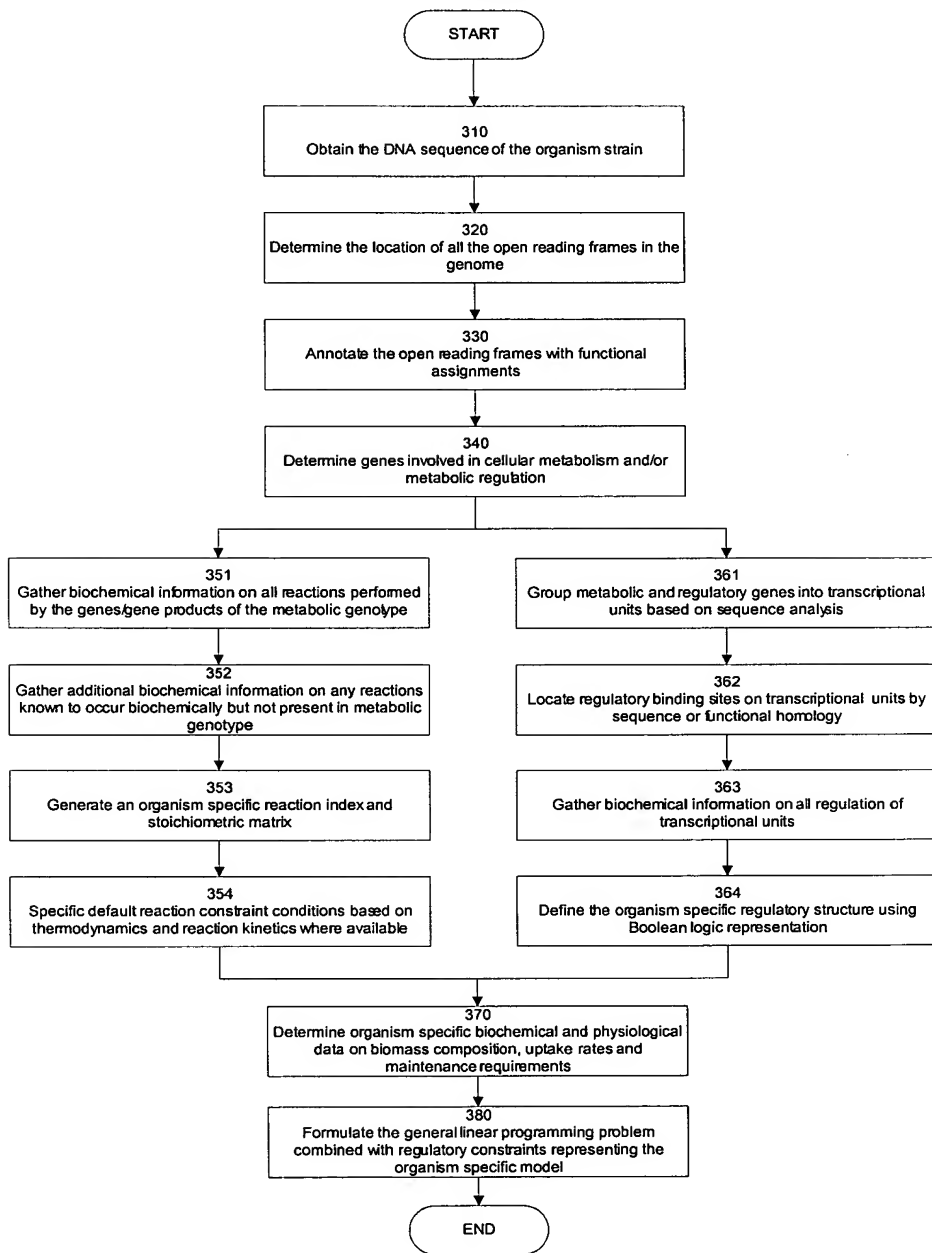


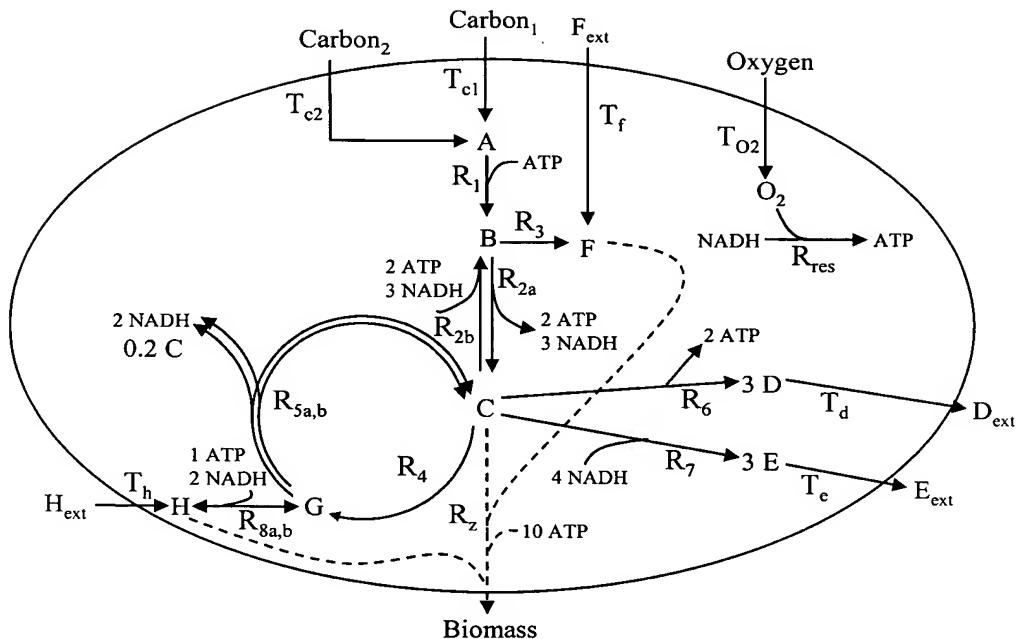
Figure 6

300
Process for Developing Genome Scale Regulated
Models of Metabolism



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Figure 7



REACTION	NAME	REGULATION
<i>Metabolic Reactions</i>		
-1 A -1 ATP +1 B	R1	
-1 B +2 ATP +2 NADH +1 C	R2a	IF NOT(RPb)
-1 C -2 ATP -2 NADH +1 B	R2b	
-1 B +1 F	R3	
-1 C +1 G	R4	
-1 G + 0.8 C +2 NADH	R5a	IF NOT (RPo2)
-1 G + 0.8 C +2 NADH	R5b	IF RPo2
-1 C +2 ATP +3 D	R6	
-1 C -4 NADH +3 E	R7	IF NOT (RPb)
-1 G -1 ATP -2 NADH +1 H	R8a	IF NOT (RPh)
+1 G +1 ATP +2 NADH -1 H	R8b	
-1 NADH -1 O ₂ +1 ATP	Rres	IF NOT (RPo2)
<i>Transport Processes</i>		
-1 Carbon1 +1 A	Tc1	
-1 Carbon2 +1 A	Tc2	IF NOT(RPc1)
-1 Fext +1 F	Tf	
-1 D +1 Dext	Td	
-1 E +1 Eext	Te	
-1 Hext +1 H	Th	
-1 Oxygen +1 O ₂	To2	
<i>Maintenance/Growth Processes</i>		
-1 C -1 F -1 H -10 ATP +1 Biomass	Growth	
<i>Regulatory Proteins</i>		
	RPo2	IF NOT(Oxygen)
	RPc1	IF Carbon1
	RPh	IF Th
	RPb	IFR2b

Figure 8

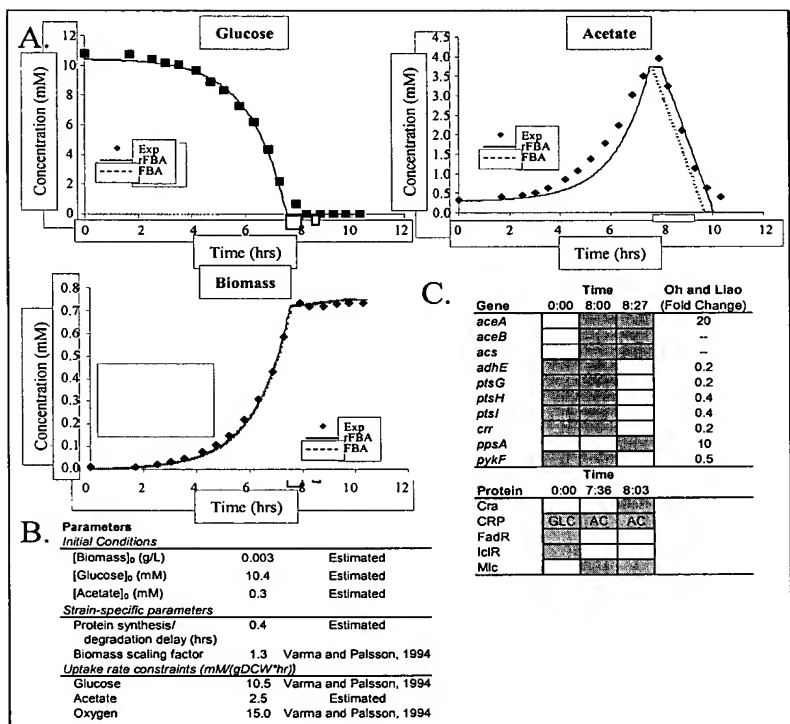


Figure 9

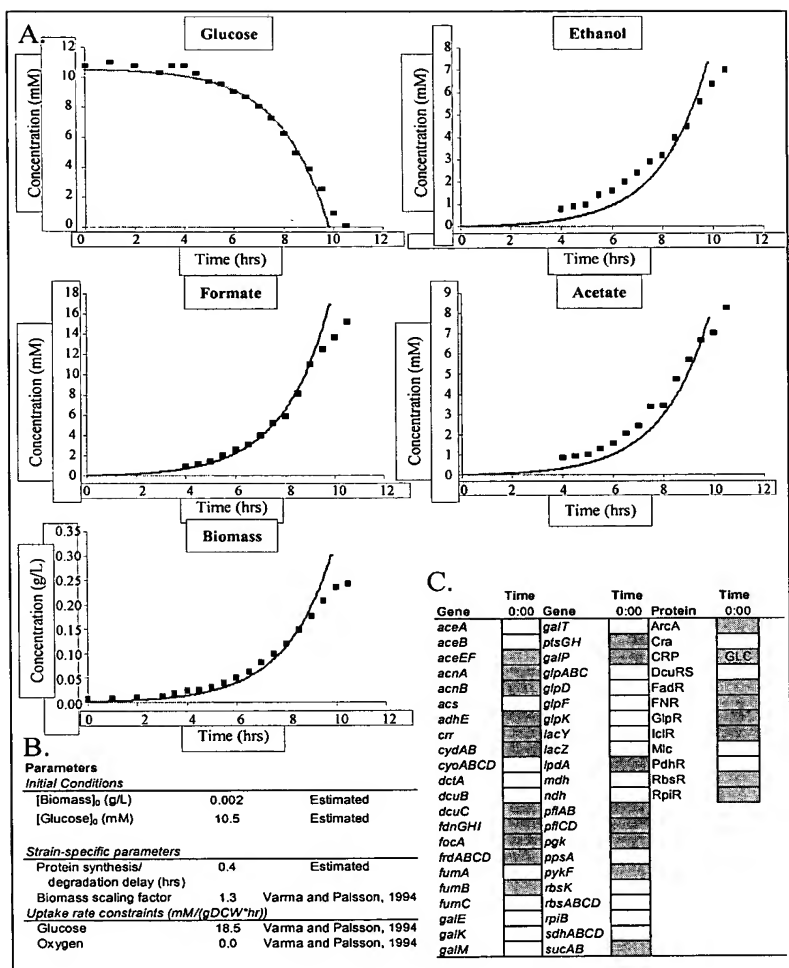


Figure 10

